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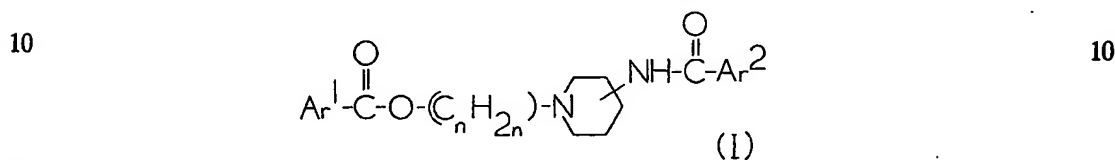
(72) Inventor: TERENCE JAMES WARD

(54) PIPERIDINE DERIVATIVES

(71) We, JOHN WYETH & BROTHER LIMITED, a British Company of Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:-

5 This invention relates to piperidine derivatives, a process for their preparation and pharmaceutical compositions containing them. 5

The invention provides novel piperidine derivatives having the formula I



15 where Ar¹ and Ar² represent aryl radicals and n denotes an integer of 2 to 6, and their acid addition salts. 15

The aryl radicals represented by Ar¹ and Ar² may be the same or different. The term "aryl" as used herein includes both carbocyclic and heterocyclic aromatic radicals. 20 Examples include thienyl, furyl, pyridyl, unsubstituted phenyl and substituted phenyl. The phenyl radical may be substituted by such substituents as halogen, for example, chlorine or bromine, lower alkyl, for example, methyl, ethyl, *n*-propyl, *i*-propyl or *n*-butyl, lower alkoxy, for example, methoxy or ethoxy, nitro, trifluoromethyl or di(lower alkyl) amino, for 25 example, dimethylamino or diethylamino. Advantageously the aryl radicals are unsubstituted phenyl. The term "lower" as used herein in connection with such groups as "alkyl" or "alkoxy" denotes that the group contains up to 6 carbon atoms, preferably up to 4 carbon atoms. 25

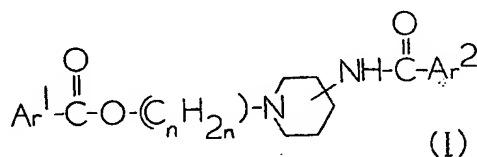
The divalent aliphatic hydrocarbon radical of the formula - (C_nH_{2n})- is preferably a straight chain but may be branched. The symbol n represents an integer from 2 to 6, 30 preferably from 2 to 4. Illustrative examples of the divalent hydrocarbon radical include ethylene, trimethylene, propylene, tetramethylene and pentamethylene. 30

The aroylamino substituent having the formula -NH-CO-Ar² is preferably at the 4-position of the piperidine ring in formula I.

35 Examples of acid addition salts are those formed from inorganic and organic acids and in particular pharmaceutically acceptable acid addition salts such as the sulphate, hydrochloride, hydrobromide, hydroiodide, nitrate, phosphate, sulphonate (such as the methane-sulphonate and *p*-toluenesulphonate), acetate, melete, fumarate, tartrate, malonate, citrate and formate. 35

40 The invention also provides a process for the preparation of a piperidine derivative having the formula I 40

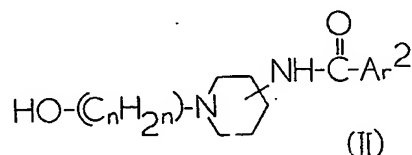
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10 (wherein Ar^1 , Ar^2 and n are as defined above) or an acid addition salt thereof, wherein
 (a) an alcohol having the formula

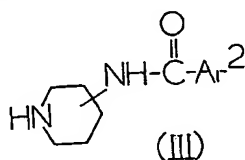
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20 (where Ar^2 and n are as defined above) or an acid addition salt thereof, is reacted with an
 acid having the formula Ar^1COOH (where Ar^1 is as defined above) or a reactive derivative
 thereof, or
 (b) a compound having the formula

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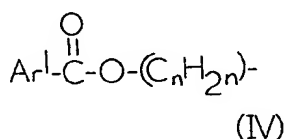


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(where Ar^2 is as defined above) or an acid addition salt thereof is alkylated with an alkylat-
 ing agent for introducing the substituted alkyl group having the formula

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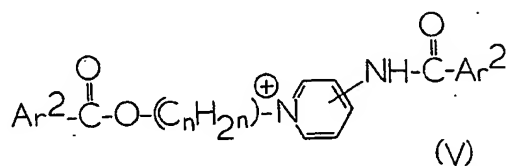


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(where Ar^1 and n are as defined above), or
 (c) a salt containing a cation having the formula V

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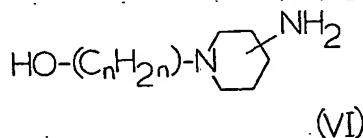


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(wherein Ar^1 , Ar^2 and n are as defined above) is reduced to convert the pyridine ring to a
 piperidine ring, or (d) a compound having the formula VI

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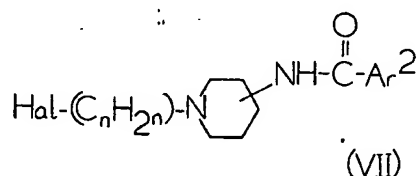
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(where n is as defined above) or an acid addition salt thereof is reacted with an acid having
 formula ArCOOH (where Ar is an aryl group) or a reactive derivative thereof, or
 (e) a compound having the formula VII

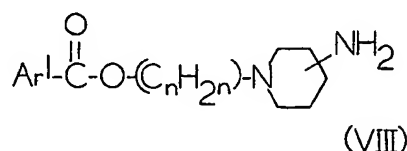
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(where Hal is a halogen atom and Ar² and n are as defined above) or an acid addition salt thereof is reacted with a suitable metal salt of an acid having formula Ar¹COOH (where Ar¹ is as defined above), or
 (f) a compound having the formula VIII



(wherein Ar¹ and n are as defined above) or an acid addition salt thereof or an activated amino derivative thereof is reacted with an acid having the formula Ar²COOH (where Ar² and n are as defined above) or a reactive derivative thereof,
 and, if desired, a free base form of a compound having formula I is converted into an acid addition salt form or an acid addition salt form of compound having formula I is converted into the free base form.

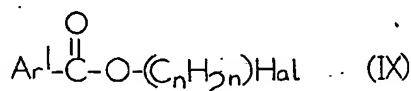
Step (a) may be carried out by reaction of the alcohol of formula II or an acid addition with the acid of formula Ar¹COOH. The esterification may be carried out in known manner. The reaction is preferably carried out in the presence of a dehydrating agent or a small amount of an acid as catalyst, for example, hydrogen chloride or concentrated sulphuric acid. An excess of the aromatic acid of formula Ar¹COOH may be used. The water formed in the reaction is preferably removed from the reaction mixture, for example, by distillation.

Instead of using the acid having formula Ar¹COOH there may be used a reactive derivative of the acid, for example, an acid halide, particularly the acid chloride or acid bromide, or the acid anhydride. Step (a) may also be carried out by transesterification using an ester of the acid Ar¹COOH with a volatile alcohol, for example, the methyl or ethyl ester. The transesterification may be carried out with a suitable catalyst, for instance, hydrogen chloride or sulphuric acid. The volatile alcohol is distilled off from the reaction mixture.

The preferred method of carrying out step (a) consisting in reacting the alcohol of formula II or an acid addition salt thereof with the acid chloride of formula Ar¹COC1 in the presence of a tertiary amine, for example, triethylamine.

The alcohols having formula II are generally known (see British Patent Specification 1,425,706). They may be prepared by reaction of a compound having the formula III with a compound having the formula Hal-(C_nH_{2n})-OH (where n is as defined above and Hal is a halogen atom, preferably chlorine or bromine). The alcohols having formula II where HO-(C_nH_{2n})- is a β-hydroxyalkyl group may also be prepared by reaction of an epoxide such as ethylene oxide or propylene oxide with a compound having formula III.

Step (b) may be carried out in conventional manner for alkylation. In particular a compound having the formula IX



(where Ar¹ and n are as defined above and Hal is a halogen atom, preferably chlorine or bromine) may be reacted with the compound of formula III in the presence of a suitable acid acceptor, for example, an amine such as triethylamine.

Step (c) resides in the reduction of a pyridine derivative to form a piperidine derivative. The reaction may be carried out by catalytic hydrogenation, for instance, using a nickel catalyst. The compound having formula V may be prepared from an aminopyridine in known manner.

The ester formation of step (a) may also be combined with an acylation step to introduce the other aroyl radical in formula I. A single reagent may be used with the result that the two aroyl radicals, Ar¹CO- and Ar²CO-, are identical. Thus, for example, step (d) may be

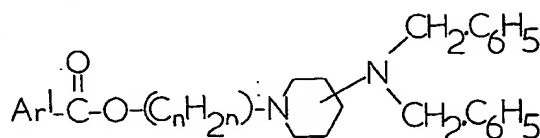
illustrated by reaction of a compound having the formula VI with an aroyl chloride in the presence of tertiary amine such as triethylamine to acylate both the amino and the hydroxyl functions of the compound having formula VI. The compound having formula VI may be prepared by alkylating a suitably protected amino piperidine to introduce the group

5 HO-(C_n the piperidine ring.

Step (e) is preferably carried out by reaction of the compound having formula VII with the silver salt of the acid of formula Ar¹COOH. The compound having formula VII may be prepared by reaction of a compound having formula II with a halogen-containing reagent that reacts with alcohols by replacing hydroxyl with halogen, for instance, thionyl chloride.

10 Step (f) may be carried out by reacting the acid having the formula Ar²COOH with the compound having formula VIII in the presence of a condensing agent, for instance, a carbodiimide. Alternatively the acid may be reacted with a derivative of the compound having formula VIII in which the amino function has been activated, for example, by forming the phosphazo derivative. The reactive acylating derivatives of the acid Ar²COOH

15 may be employed for reaction with the compound having formula VIII. Examples of such acylating derivatives include the active esters, acyl halides, simple and mixed anhydrides and the acid azide. The acid halides, particularly the acid chloride, are especially suitable. The compound having formula VIII may be prepared in known manner. In particular a compound having the formula



(where Ar¹ and n are defined above) may be built up by known reactions and the two benzyl radicals used as protecting groups may be removed by hydrogenation.

30 Acid addition salts of the compound having formula I may be converted into the free base form in known manner by neutralisation with a base. The neutralisation conditions should be mild and the free base removed from the base without delay in order to prevent possible hydrolysis of the ester. The free base may itself be converted into an acid addition salt in standard manner, e.g. by adding ethereal or ethanolic hydrogen chloride to form the hydrochloride.

35 It will be appreciated that in the process of the invention it is expedient to avoid reaction conditions such as strong aqueous alkaline conditions which will hydrolyse the ester function of the compound having formula I.

40 The piperidine derivatives having formula I and their pharmaceutically acceptable acid addition salts are useful pharmaceutically. In particular they show hypotensive activity when tested on mammals according to standard procedure.

The following test procedure may be employed:-

45 Charles River rats (200-250 g) are anaesthetised with pentobarbitone sodium (60 mg/kg i.p.). The animals are allowed to breathe spontaneously through tracheostomy tubes. Carotid arterial blood pressure is monitored and recorded. Drugs are administered via a catheter inserted in the jugular vein.

50 Control measurement of blood pressure and heart rate are taken immediately prior to and 30 seconds and 15 minutes following the injection of a dose of the test compound. The compound is administered over a cumulative dose range of 0.8-25.6 mg/kg i.v. The method is carried out in duplicate. Compounds are regarded as producing sustained hypotension if they produce a 30 mm Hg or more fall in diastolic blood pressure at 15 minutes. The compounds are regarded as showing transient hypotension if there is a 30 mm Hg or more fall at 30 seconds.

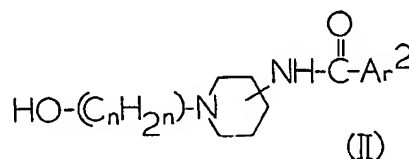
The compounds of Examples 1 and 2 produced sustained hypotension in this procedure at doses averaging about 14 mg/kg and 8 mg/kg respectively.

55 The invention also includes a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

60 In the pharmaceutical compositions of the invention the active ingredient a compound of formula (1) as hereinbefore defined, may be micronised. In addition to the active ingredient, said compositions also contain a non-toxic carrier. Any suitable carrier known in the art can be used to prepare the pharmaceutical compositions. In such a composition, the carrier may be a solid, liquid or mixture of a solid and a liquid. Solid form compositions include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, binders, or

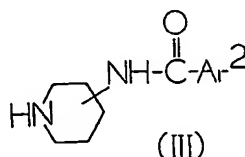
65 tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier

2. A compound as claimed in claim 1, wherein n is an integer from 2 to 4.
 3. A compound as claimed in claim 1 or 2, wherein Ar¹ and Ar² are independently thienyl, furyl, pyridyl, phenyl or substituted phenyl.
 4. A compound as claimed in claim 1 or 2 wherein Ar¹ and Ar² are each phenyl.
 5. 4-Benzamido-1- (2-benzoyloxyethyl) piperidine or an acid addition salt thereof.
 6. 4-Benzamido-1- (3-benzoyloxypropyl) piperidine or an acid addition salt thereof.
 7. A process for the preparation of a compound claimed in claim 1, wherein
 (a) an alcohol having the formula

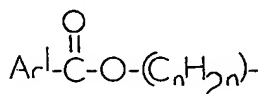


(where Ar² and n are as defined in claim 1) or an acid addition salt thereof, is reacted with an acid having the formula Ar¹COOH (where Ar¹ is as defined in claim 1) or a reactive derivative thereof, or

(b) a compound having the formula



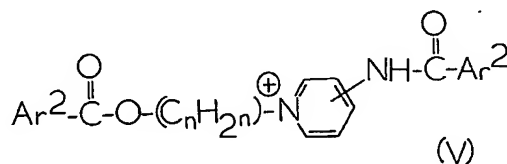
(where Ar² is as defined in claim 1) or an acid addition salt thereof is alkylated with an alkylating agent for introducing the substituted alkyl group having the formula



(IV)

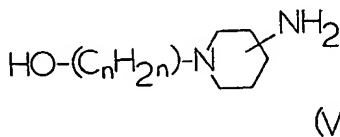
(where Ar¹ and n are as in claim 1), or

(c) a salt containing a cation having the formula V



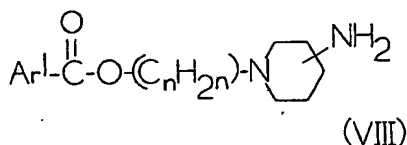
(wherein Ar¹, Ar² and n are as defined in claim 1) is reduced to convert the pyridine ring to a piperidine ring, or

(d) a compound having the formula VI



- (where n is as defined in claim 1) or an acid addition salt thereof is reacted with an acid having formula ArCOOH (where Ar is an aryl group) or a reactive derivative thereof, or
 (e) a compound having the formula VII

(where Hal is a halogen atom and Ar² and n are as defined in claim 1) or an acid addition salt thereof is reacted with a suitable metal salt of an acid having formula Ar¹COOH (where Ar¹ is as defined in claim 1), or
 (f) a compound having the formula VIII



(wherein Ar¹ and n are as defined in claim 1 or an acid addition salt thereof or an activated amino derivative thereof is reacted with an acid having the formula Ar²COOH (where Ar² and nd are as defined in claim 1) or a reactive derivative thereof, and, if desired, a free base form of a compound having formula I is converted into an acid addition salt form or an acid addition salt form of compound having formula I is converted into the free base form.

8. A process as claimed in claim 7, wherein n is an integer from 2 to 4.

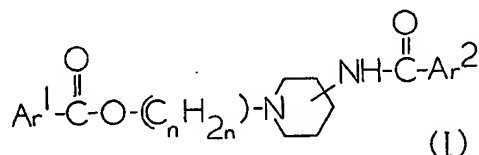
9. A process as claimed in claim 7 or 8, wherein Ar¹ and Ar² are as defined in claim 3.

10. A process as claimed in claim 7 or 8, wherein Ar¹ and Ar² are each phenyl.

11. A process as claimed in claim 7, carried out substantially as described in Example 1 or 2 herein.

12. A compound as claimed in claim 1, whenever prepared by a process as claimed in any one of claims 7 to 11.

13. A pharmaceutical composition comprising a piperidine derivative having the formula



or a pharmaceutically acceptable acid addition salt thereof, wherein Ar¹ and Ar² represent aryl radicals and n denotes an integer from 2 to 6, and a pharmaceutically acceptable carrier.

14. A composition as claimed in claim 13, wherein n is an integer from 2 to 4.

15. A composition as claimed in claim 13 or 14, wherein Ar¹ and Ar² are as defined in claim 3.

16. A composition as claimed in claim 13 or 14 wherein Ar¹ and Ar² are each phenyl.

17. A composition as claimed in claim 13, containing 4-benzamido-1-(2-benzoyloxyethyl) piperidine or a pharmaceutically acceptable acid addition salt thereof.

18. A composition as claimed in claim 13, containing 4-benzamido-1-(3-benzoyloxyp-ropyl) piperidine or a pharmaceutically acceptable acid addition salt thereof.

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 Agent for the Applicants.